



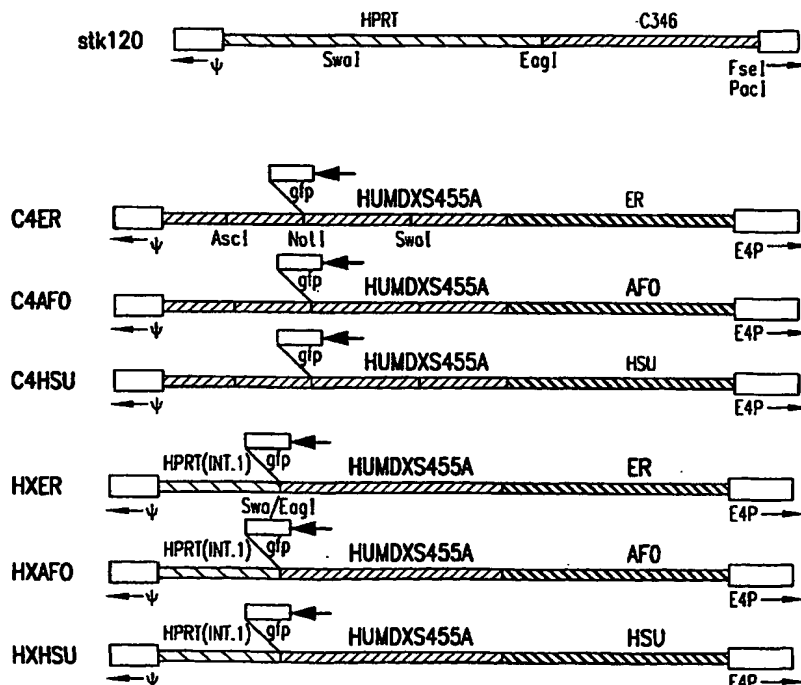
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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|---|--|---|---|
| (51) International Patent Classification ⁷ : C12N 15/00, 5/00, C07H 21/04 | | A1 | (11) International Publication Number: WO 00/46360 |
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(54) Title: IMPROVED HELPER DEPENDENT VECTOR SYSTEM FOR GENE THERAPY

(57) Abstract

The present invention features helper-dependent adenoviral vector elements, and helper adenoviral elements, that enhance the production and isolation of helper-dependent adenoviral vectors. Such elements include a modified packaging signal having low homology to, and preferably less activity than, a wild-type packaging signal, an E4 non-coding segment directly joined to the 5' ITR that confers a selective advantage, and stuffer region(s) that provide a helper-dependent adenoviral vector with a GC content of about 50 % to about 60 %. The modified packaging signal is preferably used in a helper virus to decrease recombination and generation of the virus. The E4 non-coding segment and the stuffer region(s) are preferably used in a helper-dependent adenoviral vector to provide the vector with a growth advantage over a helper virus.



PATENT COOPERATION TREATY

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(PCT Rule 61.2)

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| Date of mailing (day/month/year) 10 October 2000 (10.10.00) | |
| International application No. PCT/US00/02405 | Applicant's or agent's file reference PCT 20377Y |
| International filing date (day/month/year) 31 January 2000 (31.01.00) | Priority date (day/month/year) 04 February 1999 (04.02.99) |
| Applicant BETT, Andrew et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
25 August 2000 (25.08.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference PCT 20377Y | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US00/02405 | International filing date (day/month/year) 31 JANUARY 2000 | Priority date (day/month/year) 04 FEBRUARY 1999 |
| International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/00, 5/00; C07H 21/04 and US Cl.: 435/320.1, 325, 457; 536/23.1 | | |
| Applicant MERCK & CO., INC. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
- ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|--|---|
| Date of submission of the demand 25 AUGUST 2000 | Date of completion of this report 19 SEPTEMBER 2000 |
| Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 | Authorized officer <i>Gerald G. Leffers Jr.</i> GERALD G. LEFFERS JR. |
| Facsimile No. (703) 305-3230 | Telephone No. (703) 308-0196 |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/02405

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed☒ the description:pages 1-69, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the claims:pages 70-75, as originally filedpages NONE, as amended (together with any statement) under Article 19pages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the drawings:pages 1-8, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the sequence listing part of the description:pages 1-22, as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☒ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.4. ☒ The amendments have resulted in the cancellation of:☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig NONE5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/02405

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

| | | |
|-------------------------------|--------------------|-----|
| Novelty (N) | Claims <u>1-41</u> | YES |
| | Claims <u>NONE</u> | NO |
| Inventive Step (IS) | Claims <u>1-41</u> | YES |
| | Claims <u>NONE</u> | NO |
| Industrial Applicability (IA) | Claims <u>1-41</u> | YES |
| | Claims <u>NONE</u> | NO |

2. citations and explanations (Rule 70.7)

Claims 1-41 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the recombinant nucleic acids, adenoviral helper viruses, cell lines, adenoviral vectors and methods of generating helper-dependent adenoviral vectors recited in claims 1-41.

----- NEW CITATIONS -----
NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/02405

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:

NONE


FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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INTERNATIONAL SEARCH REPORT

 International application No.
 PCT/US00/02405

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|---|---|-----------------------|
| A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : C12N 15/00, 5/00; C07H 21/04 US CL : 435/320.1, 325, 457; 536/23.1 According to International Patent Classification (IPC) or to both national classification and IPC | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 435/320.1, 325, 457; 536/23.1 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) MEDLINE, BIOSIS, EMBASE, CAPLUS, EAST search terms: inventor's names, recombinase, cre, loxP, frt, flp, packaging, site, sequence, signal, gc content, adenovirus, helper | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT | | |
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y, P | US 5,919,676 A (GRAHAM et al) 06 JULY 1999 (06.07.1999) see entire document. | 1-41 |
| Y | WO 97/32481 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 12 SEPTEMBER 1997 (12.09.1997) see entire document, especially page 39, lines 5-20. | 1-41 |
| T | SANDIG et al. Optimization of the helper-dependent adenovirus system for production and potency <i>in vivo</i> . Proceedings of the National Academy of Sciences, USA. 01 February 2000. Vol. 97, No. 3, pages 1002-1007, see entire document. | 1-41 |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex. | | |
| * Special categories of cited documents: | *T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention | |
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| *P document published prior to the international filing date but later than the priority date claimed | | |
| Date of the actual completion of the international search 06 APRIL 2000 | Date of mailing of the international search report 25 APR 2000 | |
| Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230 | Authorized officer GERALD G. LEFFERS JR.  Telephone No. (703) 308-0196 | |